# Simultaneous fitting of the Minimal Model to IVGTT & Glucose Clamp Data

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## Introduction

The minimal model of glucose kinetics developed by Bergman et al in 1979[1] has been extensively used to provide quantitative estimates of insulin sensitivity and glucose effectiveness in both healthy and diabetic subjects. it has previously been shown that the minimal model can be successfully fitted to data from an intravenous glucose tolerance test (IVGTT) and data from a glucose clamp experiment. Here is presented the findings of fitting the minimal model to IVGTT and clamp data alone and a novel approach of fitting the minimal model simultaneously to both IVGTT and clamp data.

## Methods

### IVGTT and Clamp Study

Data from a two-period euglycaemic clamp study performed in 28 healthy volunteers was used. An IVGTT was performed prior to the first clamp period during which 0.3 g/kg of a 20% glucose solution was administered. Blood samples were then taken at –15, -5, 0, 2, 4, 6, 10, 15, 20, 25, 30, 40 minutes and 1, 1.33, 2, 3 and 4 hours post glucose dose to measure the insulin and glucose concentrations. In each of the two clamp periods of the study, a single s.c. dose of 0.2 IU/kg Actrapid® was administered. Blood glucose concentration was monitored every five minutes using HemoCue® measurements for the duration of the 8-hour clamp. Based on these glucose concentration measurements the amount of glucose to be infused to keep glucose at the clamp target value and this was determined using the manual clamping method. The measurement of blood glucose levels prior to treatment administration allowed the fasting blood glucose level of each individual, on each day of administration to be measured, this was used as the target clamp glucose concentration. Blood samples for the measurement of insulin and C-peptide were taken at 0, 0.25,0.5, 0.75, 1, 1.17, 1.33, 1.5, 1.67, 1.83, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7 and 8 hours post dose with time 0 being immediately prior to insulin administration on dosing day in each period. Blood samples taken at the above times were also measured in the laboratory for the blood glucose concentration in addition to the bedside HemoCue® glucose measurements.

The mean and individual glucose, insulin and GIR against time profiles from the IVGTT and clamps are shown in Figures 1-5.

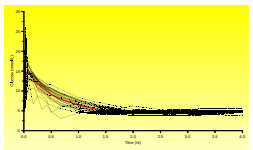

Figure 1 – Individual (dotted) and mean (red) glucose-time profiles in the IVGTT

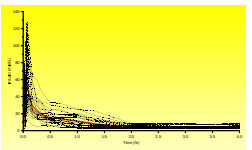

Figure 2 - Individual (dotted) and mean (red) insulin-time profiles in the IVGTT

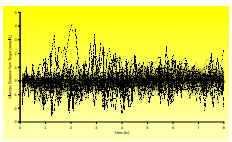

Figure 3 – Individual (dotted) glucose distance from target-time for the two clamp periods

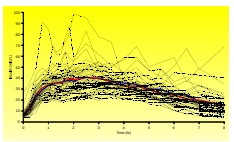

Figure 4 - Individual (dotted) and mean (Actrapid® 1 – Red, Actrapid® 2 – Blue) insulin-time profiles for the two clamp periods

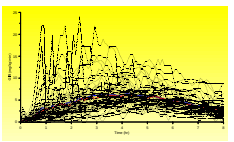

Figure 4 - Individual (dotted) and mean (Actrapid® 1 – Red, Actrapid® 2 – Blue) GIR-time profiles for the two clamp periods

### Minimal Model

The minimal model as presented by Vicini *et al*[2] is shown in Figure 6 with its uniquely identifiable parameterisation described in Figure 7.

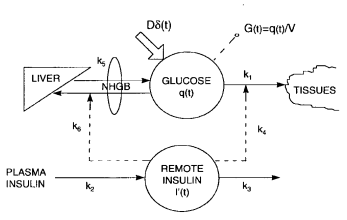


Figure 6 – Diagram of the Minimal Model

$$\frac{dq(t)}{dt} = -[S_G + x(t)]q(t) + S_G G_b V_G + D\delta(t) \qquad q0 = q_{1b} = G_b V_G$$

$$\frac{dx(t)}{dt} = -p_2\{x(t) - S_I[I(t) - I_b]\} \qquad x(0) = 0$$

$$G(t) = \frac{q(t)}{V_G}$$

Figure 7 – Equations of the Minimal Model

Where $G_b$ is the basal plasma glucose concentration, $I_b$ is the basal insulin plasma concentration, $q$ is glucose mass, $I(t)$ is insulin plasma concentration, $G(t)$ is glucose plasma concentration, $V_G$ the glucose volume of distribution, $x$ and $p_2$ describe insulin action, $D\delta(t)$ is the dose of glucose. $S_I$ describes the insulin sensitivity - the ability of insulin to enhance glucose disposal and inhibit glucose production. $S_G$ describes the glucose effectiveness - the ability of glucose to stimulate glucose disposal and inhibit endogenous glucose production. NHGB refers the net hepatic glucose balance.

### Data fitting Methods and Fisher Information Matrix (FIM)

Model fitting and minimal model parameter values were estimated using the first order estimation method in NONMEM®. Four parameters were estimated $S_I$, $S_G$, $V_G$ & $p_2$. $G_b$ and $I_b$ along with the observed insulin concentrations were supplied in the dataset. The NONMEM® estimates were used to compute the FIM for the fixed effect parameters ($S_I$, $S_G$, $V_G$ & $p_2$) using Matlab®.

## Results

Parameter estimates are presented in Table 1 for fitting of the minimal model to the three types of data: IVGTT alone, clamp alone and IVGTT & clamp together. Plots of observed glucose concentrations versus population and individual predictions and time are presented in Figures 8 & 9 for the clamp only data and in Figures 10 & 11 for the simultaneous fit of IVGTT and clamp data. Parameter estimates for the simultaneous fit of IVGTT and Period 1 clamp data were used to predict the glucose concentrations for the second clamp period. Figure 12 shows some individual observed and predicted Period 2 glucose concentrations. Results from the FIM are presented in Table 2.

Table 1 – Results of fitting the minimal model to IVGTT, clamp and both IVGTT and clamp data

| Minimal Model Parameter | Population Parameter Estimate (CV%) | | | |
|---|---|---|---|---|
| | IVGTT alone | Clamp alone | Simultaneous IVGTT & Clamp | |
| | | | Period 1 Clamp Data | Period 2 Clamp Data |
| $S_I$ ($min^{-1}$ per $mU.L^{-1}$) | NC | 0.000439 (26.7) | 0.00134 (12.4) | 0.00107 (17.1) |
| $S_G$ ($min^{-1}$) | NC | 0.0568 (14.7) | 0.0183 (10.7) | 0.0120 (16.5) |
| $V_G$ (L/kg) | NC | 0.472 (32.6) | 0.164 (6.0) | 0.171 (3.0) |
| $p_2$ ($min^{-1}$) | NC | 0.0170 (20.4) | 0.0138 (17.0) | 0.0180 (22.3) |

### Clamp only data

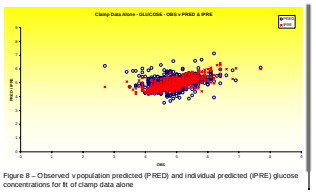

Figure 8 – Observed v population predicted (PRED) and individual predicted (IPRE) glucose concentrations for fit of clamp data alone

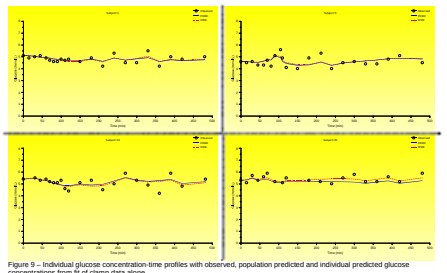

Figure 9 – Individual glucose concentration-time profiles with observed, population predicted and individual predicted glucose concentrations from fit of clamp data alone

### IVGTT & Clamp Simultaneous data

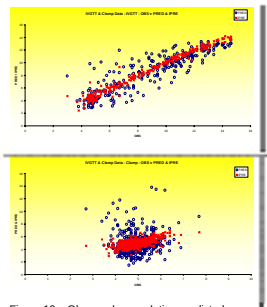

Figure 10 – Observed v population predicted (PRED) and individual predicted (IPRE) glucose concentrations for fit of IVGTT & clamp data

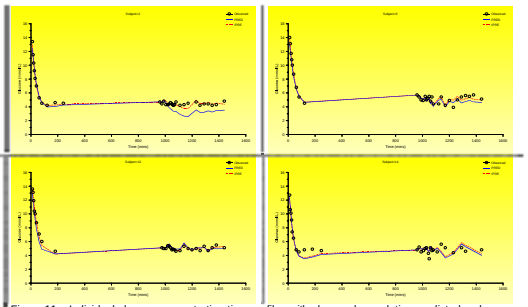

Figure 11 – Individual glucose concentration-time profiles with observed, population predicted and individual predicted glucose concentrations from fit of IVGTT & clamp data

### Prediction of Period 2 glucose clamp data

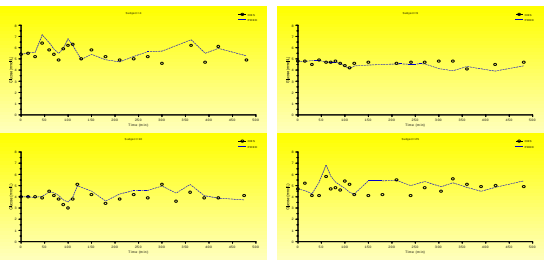

Figure 12 – Observed and predicted glucose concentrations for clamp Period 2 with concentrations predicted by the minimal model using parameter estimates from fitting of Period 1 IVGTT and Clamp data

### Fisher Information Matrix

Table 2 – Results of the Fisher Information Matrix

| Type of Data | Minimal Model Parameter CV% | | | |
|---|---|---|---|---|
| | $V_G$ | $S_G$ | $S_I$ | $p_2$ |
| IVGTT alone | 1.045 | 9.606 | **42.970** | **46.456** |
| Clamp alone (insulin times) | 1.721 | 10.314 | 5.506 | 11.217 |
| Clamp alone (Hemacue® times) | 0.784 | 2.660 | 2.177 | 3.247 |
| Simultaneous (IVGTT and Clamp) | 0.437 | 0.892 | **1.655** | **0.958** |

## Conclusion

- As indicated by the FIM, minimal model parameters were estimable from fitting to clamp data alone and by simultaneous fitting to both IVGTT and clamp data. Fitting of IVGTT alone was not successful as the parameters SI and p2 were unidentifiable, again as indicated by the FIM.
- Addition of the IVGTT data to the clamp data stabilised the fitting with reliable and consistent parameter estimates obtained from the simultaneous fit

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**References:** [1] Bergman *et al* (1979). *Am J Physiol*. 236: E667-677. [2] Vicini *et al* (1999). *IEEE Trans Biomed Eng*. 46: 130-137.